JUL 11 2000

NDA 20-545/S-004

King Pharmaceuticals, Inc.
Attention: Ms. Suzanne B. Smith
501 Fifth Street
Bristol, Tennessee 37620

Dear Ms. Smith:

Please refer to your supplemental new drug application dated October 8, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Procanbid (procainamide HCl) Extended-Release Tablets.

We acknowledge receipt of your submission dated May 2, 2000 that constituted a complete response to our February 12, 1999 approvable letter.

This supplemental new drug application provides for final printed labeling revised as follows:

1. A **Geriatric Use** subsection was added to the **PRECAUTIONS** section:

   Geriatric Use: Clinical studies of procainamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to the drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function by calculating creatinine clearance and to monitor the plasma levels of procainamide and its major metabolite, N-acetyl procainamide.

2. Under **DESCRIPTION,**

   a) The sentence “Both strengths of Procanbid® contain this PolymatrixTM core.” has been added to the third paragraph.

   b) The second to the last sentence in the third paragraph has been deleted. This sentence stated:

      The 500-mg tablet additionally contains FD&C blue No. 1 aluminum lake.

3. Under **HOW SUPPLIED,**

a) The color for the 500 mg tablet has been changed from blue to white.

b) The NDC numbers for the 500 and 1000 mg tablets have been changed. These numbers have changed from:

500mg
N 007 1-0562-20 Bottles of 60
N 0071-0562-40 Unit dose packages of 100 (10 strips of 10 tablets each)

1000mg
N 0071-0564-20 Bottles of 60
N 0071-0564-40 Unit dose packages of 100 (10 strips of 10 tablets each)

to:

500mg
NDC 61570-069-60 Bottles of 60
NDC 61570-069-70 Unit dose packages of 100 (10 strips of 10 tablets each)

1000 mg
NDC 61570-071-60 Bottles of 60
NDC 61570-071-70 Unit dose packages of 100 (10 strips of 10 tablets each)

c) The "Caution – Federal law prohibits dispensing without prescription" statement has been changed to "Rx Only."

d) The sponsor name and distributed by have been changed from:

PARKE-DAVIS
Div of Wamer-Lambert Co
Morris Plains, NJ 07950 USA

to:

Monarch Pharmaceuticals

Distributed by:
Monarch Pharmaceuticals, Inc.
Bristol, TN 37620
Manufactured by:
Wamer-Lambert Co
Morris Plains, NJ 07950 USA

4. There were minor editorial changes throughout the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included your submission dated May 2, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Procanbid®

(Procainamide Hydrochloride Extended-Release Tablets*)

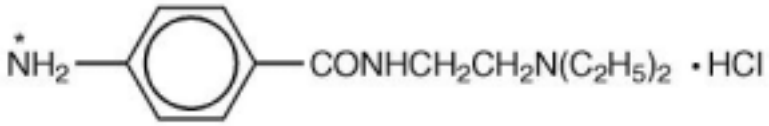
*Procanbid is not USP for dissolution

WARNINGS:

Positive ANA Titer: The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test, with or without symptoms of a lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefits versus risks of continued procainamide therapy should be assessed.

DESCRIPTION

Procanbid (Procainamide Hydrochloride Extended-Release Tablets), a Group 1A cardiac antiarrhythmic drug, is p-amino-N-[2-(diethylamino) ethyl]benzamide monohydrochloride, molecular weight 271.79. Its structural formula is:



(*Site of acetylation to N-acetylprocainamide)

Procainamide hydrochloride differs from procaine which is the p-aminobenzoyl ester of 2-(diethylamino)ethanol. Procainamide as the free base has a pK_a of 9.24; the monohydrochloride is very soluble in water.

Procanbid (Procainamide Hydrochloride Extended-Release Tablets) contains 500 mg or 1000 mg of procainamide hydrochloride for oral administration. The release of procainamide hydrochloride is controlled by 2 mechanisms using patented technology. The core of the tablet consists of a wax matrix which is then coated with a polymeric, control-release layer. Both strengths of Procanbid® contain this Polymatrix™ core. Both strengths of Procanbid contain black iron oxide; candelilla wax, FCC; carnauba wax, NF; colloidal silicon dioxide, NF; hydroxypropyl cellulose, NF; hydroxypropylmethyl cellulose; magnesium stearate, NF; polyacrylate dispersion; polyethylene glycol 3350, NF; polyethylene glycol 8000, NF; propylene glycol; simethicone emulsion, USP; talc, USP; and titanium dioxide. The 1000-mg tablet additionally contains polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action: Procainamide (PA) increases the effective refractory period of the atria, and to a lesser extent the bundle of His-Purkinje system and ventricles of the heart. It reduces impulse conduction velocity in the atria, His-Purkinje fibers, and ventricular muscle, but has variable effects on the atrioventricular (A-V) node, a direct slowing action and a weaker vagolytic effect that may speed A-V conduction slightly. Myocardial excitability is reduced in the atria, Purkinje fibers, papillary muscles, and ventricles by an increase in the threshold for excitation, combined with inhibition of ectopic pacemaker activity by retardation of the slow phase of diastolic depolarization, thus decreasing automaticity especially in ectopic sites. Contractility of the undamaged heart is usually not affected by therapeutic concentrations, although slight reduction of cardiac output may occur, and may be significant in the presence of myocardial damage. Therapeutic levels of PA may exert vagolytic effects and produce slight acceleration of heart rate, while high or toxic concentrations may prolong A-V conduction time or induce A-V block, or even cause abnormal automaticity and spontaneous firing, by unknown mechanisms.

The electrocardiogram may reflect these effects by showing slight sinus tachycardia (due to the anticholinergic action) and widened QRS complexes and, less regularly, prolonged Q-T and P-R intervals

(due to longer systole and slower conduction), as well as some decrease in QRS and T wave amplitude. These direct effects of PA on electrical activity, conduction, responsiveness, excitability, and automaticity are characteristic of a Group 1A antiarrhythmic agent, the prototype for which is quinidine; PA effects are very similar. However, PA has weaker vagal blocking action than does quinidine, does not induce alpha-adrenergic blockade, and is less depressing to cardiac contractility.

Pharmacokinetics and Drug Metabolism

Absorption/Bioavailability: PA is well absorbed following oral administration. The absolute bioavailability from immediate-release PA HCl capsules is approximately 85% in patients and healthy subjects. Bioavailability of Procanbid is similar to that of PA HCl extended-release tablets, USP (Procan®SR) which have been shown to be similar to that of immediate-release PA.

The Procanbid patented delivery system is designed to control the rate of PA release such that absorption is sustained throughout a 12-hour dosing interval. After administration of Procanbid with a high-fat meal, the extent of PA absorption was increased by about 20%. Peak, trough, and average plasma PA concentrations following twice daily administration of Procanbid to healthy subjects are similar to those achieved when Procan SR is administered 4 times daily. In patients with frequent ventricular premature depolarizations (VPDs), peak and steady-state average PA concentrations following administration of Procanbid every 12 hours are bioequivalent to those following administration of an equivalent daily dose of Procan SR. While corresponding minimum concentrations are slightly lower than those for Procan SR, they remain within the acceptable therapeutic range of 3 to 10 mcg/mL.

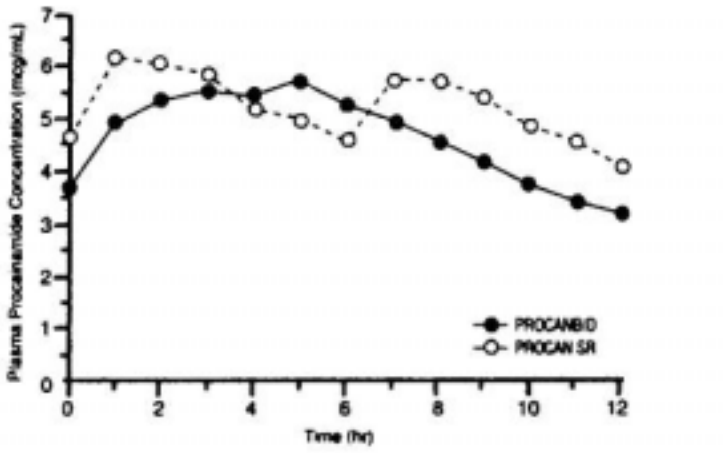


Figure 1. Mean Steady-State Plasma Concentrations Following Administration of Two 1000-mg Procanbid Tablets Every 12 Hours or One 1000-mg Procan SR Tablet Every 6 Hours to Patients with VPDs.

Twice-daily administration of two 1000-mg Procanbid tablets to patients with frequent VPDs produced a mean plasma PA concentration of 4.6 mcg/mL. Average peak and trough levels are within the generally accepted therapeutic range of 3 to 10 mcg/mL. Relative proportions of PA and N-acetylprocainamide (NAPA) during administration of Procanbid are similar to those following administration of immediate-release PA or Procan SR.

Distribution: Plasma protein binding of PA is insignificant, approximately 20%. The apparent volume of distribution is approximately 2 L/kg. It is not known if PA crosses the placenta.

Metabolism/Excretion: The elimination half-life of PA is 3 to 4 hours in patients with normal renal function, but reduced renal function prolongs the half-life (see Special Populations). PA is mainly eliminated intact by the kidneys. The only metabolite of any significance is N-acetylprocainamide (NAPA). Renal excretion accounts for >80% of the elimination of NAPA. Approximately 16 to 21% of PA is

metabolized to NAPA in "slow acetylators"; in "rapid acetylators" the range is 24 to 33%. In white and black populations the numbers of rapid and slow acetylators are about 50%. The plasma concentration of NAPA is lower than the PA concentration in most individuals. The reverse may occur in individuals forming more of the metabolite while also having reduced kidney function. NAPA has significant antiarrhythmic activity.
An average of 65% of the dose was recovered as intact drug in the urine after intravenous administration of PA. The renal clearance of PA ranged from 400 to 600 mL/min. Active renal secretion ranged from 300 to 500 mL/min, and is thus the major elimination pathway for PA. The tubular secretion utilizes the base-secreting system also responsible for secretion of metformin, cimetidine, ranitidine, triamterene, and flecainide. Thus there is a potential for drug-drug interactions at this level.

Special Populations: *Patients with Renal Disease:* Decline in renal function, such as that occurring with advancing age or renal disease, increases the PA elimination half-life which can result in relatively high plasma concentrations of PA (see WARNINGS). Accumulation of NAPA due to impaired renal function can be more extensive than accumulation of PA.

Patients with Congestive Heart Failure: PA clearance is reduced in patients with severe heart failure, in part due to decreased renal perfusion (see WARNINGS).

Age, Gender, and Race: PA clearance decreases with increasing patient age, in part due to concurrent decreases in renal function. However, the pharmacokinetics of PA and NAPA are similar in young healthy subjects (mean age 32 yr) and patients with frequent VPDs (mean age 60 yr) following administration of Procanbid every 12 hours. Steady state plasma procainamide concentrations in women receiving Procanbid are 30 percent higher than those seen in men receiving the same dosing regimen. When corrected for body surface area this difference is only 16 percent. Concentrations of N-acetylprocainamide are not significantly different among men and women whether corrected for body surface area or not. Procanbid tablets produce similar PA and NAPA concentrations in black and caucasian individuals.

Pharmacodynamics: While therapeutic plasma PA concentrations have been reported to be 3 to 10 mcg/mL, patients such as those with sustained ventricular tachycardia may need higher concentrations for adequate control. This may justify an increased risk of toxicity (see OVERDOSAGE). Where programmed ventricular stimulation has been used to evaluate efficacy of PA in preventing recurring ventricular tachyarrhythmias, an average plasma PA concentration of 13.6 mcg/mL was necessary for adequate control. Action of PA on the central nervous system is not prominent, but high concentrations may cause tremors.
A double-blind, placebo-controlled, dose-response, formulation-crossover study was conducted, comparing the suppression of VPDs by Procanbid administered every 12 hours and Procan SR administered every 6 hours. Similar VPD suppression was observed following administration of both formulations for 1 week each. Procanbid demonstrated significant pharmacologic activity (mean percent change from baseline in VPDs) compared with placebo, and a significant linear dose-response relationship was observed. VPD suppression was maintained throughout the dosing interval.
In this study, VPD rate tended to decrease with increasing concentration of PA and NAPA; however, PA concentration alone was a poor predictor of antiarrhythmic effect. The concentration-effect relationship for administration of Procanbid every 12 hours was indistinguishable from that for administration of Procan SR every 6 hours.

INDICATIONS AND USAGE

Procanbid tablets are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life-threatening. Because of the proarrhythmic effects of procainamide, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature depolarizations should be avoided.
Initiation of procainamide treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.
Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.
Because procainamide has the potential to produce serious hematologic disorders (0.5%), particularly leukopenia or agranulocytosis (sometimes fatal), its use should be reserved for patients in whom, in the

opinion of the physician, the benefits of treatment clearly outweigh the risks. (See WARNINGS and Boxed Warning .)

CONTRAINDICATIONS

Complete Heart Block: Procainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during PA treatment without evidence of A-V conduction appearing, PA should be stopped. In cases of second degree A-V block or various types of hemiblock, PA should be avoided or discontinued because of the possibility of increased severity of block unless the ventricular rate is controlled by an electrical pacemaker.

Idiosyncratic Hypersensitivity: In patients sensitive to procaine or other ester-type local anesthetics, cross sensitivity to PA is unlikely; however, it should be borne in mind, and PA should not be used if it produces acute allergic dermatitis, asthma, or anaphylactic symptoms.

Lupus Erythematosus: An established diagnosis of systemic lupus erythematosus is a contraindication to PA therapy, since aggravation of symptoms is highly likely.

Torsades De Pointes: In the unusual ventricular arrhythmia called "les torsades de pointes" (twisting of the points), characterized by alternation of 1 or more ventricular premature beats in the directions of the QRS complexes on ECG in persons with prolonged Q-T and often enhanced U waves, Group 1A antiarrhythmic drugs are contraindicated. Administration of PA in such cases may aggravate this special type of ventricular extrasystole or tachycardia instead of suppressing it.

WARNINGS

Mortality: In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppresion Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was 10 months.

The applicability of the CAST results to other populations (eg, those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of procainamide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of Procanbid as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

BLOOD DYSCRASIAS: Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia, and thrombocytopenia have been reported in patients receiving procainamide hydrochloride at a rate of approximately 0.5%. Most of these patients received procainamide hydrochloride within the recommended dosage range. Fatalities have occurred (with approximately 20%-25% mortality in reported cases of agranulocytosis). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts including white cell, differential, and platelet counts be performed at weekly intervals for the first 3 months of therapy, and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders are identified, procainamide hydrochloride should be discontinued. Blood counts usually return to normal within 1 month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type (see ADVERSE REACTIONS).

Digitalis Intoxication: Caution should be exercised in the use of procainamide in arrhythmias associated with digitalis intoxication. Procainamide can suppress digitalis-induced arrhythmias; however, if there is concomitant marked disturbance of atrioventricular conduction, additional depression of conduction and ventricular asystole or fibrillation may result. Therefore, use of procainamide should be considered only if discontinuation of digitalis, and therapy with potassium lidocaine, or phenytoin are ineffective.

First Degree Heart Block: Caution should be exercised also if the patient exhibits or develops first degree heart block while taking PA, and dosage reduction is advised in such cases. If the block persists despite dosage reduction, continuation of PA administration must be evaluated on the basis of current benefit versus risk of increased heart block.

Predigitalization for Atrial Flutter or Fibrillation: Patients with atrial flutter or fibrillation should be cardioverted or digitalized prior to PA administration to avoid enhancement of A-V conduction which may result in ventricular rate acceleration beyond tolerable limits. Adequate digitalization reduces but does not eliminate the possibility of sudden increase in ventricular rate as the atrial rate is slowed by PA in these arrhythmias.

Congestive Heart Failure: For patients in congestive heart failure, and those with acute ischemic heart disease or cardiomyopathy, caution should be used in PA therapy, since even slight depression of myocardial contractility may further reduce the cardiac output of the damaged heart.

Concurrent Other Antiarrhythmic Agents: Concurrent use of PA with other Group 1A antiarrhythmic agents such as quinidine or disopyramide may produce enhanced prolongation of conduction or

depression of contractility and hypotension, especially in patients with cardiac decompensation. Such use should be reserved for patients with serious arrhythmias unresponsive to a single drug and employed only if close observation is possible.

Renal Insufficiency: Renal insufficiency may lead to accumulation of high plasma concentrations of PA and/or NAPA from conventional oral doses of PA, with effects similar to those of overdosage (see OVERDOSAGE), unless dosage is adjusted for the individual patient.

Myasthenia Gravis: Patients with myasthenia gravis may show worsening of symptoms from PA due to its procaine-like effect on diminishing acetylcholine release at skeletal muscle motor nerve endings, so that PA administration may be hazardous without optimal adjustment of anticholinesterase medications and other precautions.

PRECAUTIONS

General: Immediately after initiation of PA therapy, patients should be closely observed for possible hypersensitivity reactions, especially if procaine or local anesthetic sensitivity is suspected, and for muscular weakness if myasthenia gravis is a possibility.
In conversion of atrial fibrillation to normal sinus rhythm by any means, dislodgment of mural thrombi may lead to embolization, which should be kept in mind.
Based upon the approximate half-life of 3 hours for PA, pharmacokinetic steady state would be reached within 1 day. After achieving and maintaining therapeutic plasma concentrations and satisfactory electrocardiographic and clinical responses, continued frequent periodic monitoring of vital signs and electrocardiograms is advised. If evidence of QRS widening of more than 25% or marked prolongation of the Q-T interval occurs, concern for overdosage is appropriate, and reduction in dosage is advisable if a 50% increase occurs. Elevated serum creatinine or urea nitrogen, reduced creatinine clearance, or history of renal insufficiency, as well ase use in older patients (over age 50), provide grounds to anticipate that less than the usual dosage may suffice, since the urinary elimination of PA and NAPA may be reduced, leading to gradual accumulation beyond normally predicted amounts. If facilities are available for measurement of plasma PA and NAPA, or acetylation capability, individual dose adjustment for optimal therapeutic concentrations may be easier, but close observation of clinical effectiveness is the most important criterion.
In the longer term, periodic complete blood counts are useful to detect possible idiosyncratic hematologic effects of PA on neutrophil, platelet, or red cell homeostatis; agranulocytosis has been reported to occur occasionally in patients on long-term PA therapy. A rising titer of serum ANA may precede clinical symptoms of the lupoid syndrome (see Boxed Warning and ADVERSE REACTIONS). If the lupus erythematosus-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controlled by other agents, corticosteroid suppressive therapy may be used concomitantly with PA. Since the PA-induced lupoid syndrome rarely includes dangerous pathologic renal changes, PA therapy may not necessarily have to be stopped unless the symptoms of serositis and the possibility of further lupoid effects are of greater risk than the benefit of PA in controlling arrhythmias. Patients with rapid acetylation capability are less likely to develop the lupoid syndrome after prolonged PA therapy.

Information for Patients: The physician is advised to explain to the patient that close cooperation in adhering to the prescribed dosage schedule is of great importance in controlling the cardiac arrhythmia safely. The patient should understand clearly that more medication is not necessarily better and may be dangerous, that skipping doses or increasing intervals between doses to suit personal convenience may lead to loss of control of the heart problem, and that "making up" missed doses by doubling up later may be hazardous.
The patient should be encouraged to disclose any past history of drug sensitivity, especially to procaine or other local anesthetic agents, and to report any history of kidney disease, congestive heart failure, myasthenia gravis, liver disease, or lupus erythematosus.
The patient should be counseled to report promptly any symptoms of arthralgia, myalgia, fever, chills, skin rash, easy bruising, sore throat or sore mouth, infections, dark urine or icterus, wheezing, muscular weakness, chest or abdominal pain, palpitations, nausea, vomiting, anorexia, diarrhea, hallucinations, dizziness, or depression.

The patient should be advised not to break or chew the tablet as this would interfere with designed dissolution characteristics. The tablet matrix or Procanbid may be seen in the stool since it does not disintegrate following release of procainamide.

Laboratory Tests: Laboratory tests such as complete blood count (CBC), electrocardiogram, and serum creatinine or urea nitrogen may be indicated, depending on the clinical situation, and periodic rechecking of the CBC and ANA may be helpful in early detection of untoward reactions.

Drug Interactions: If other antiarrhythmic drugs are being used, additive effects on the heart may occur with PA administration, and dosage reduction may be necessary (see WARNINGS).
Anticholinergic drugs administered concurrently with PA may produce additive antivagal effects on A-V nodal conduction, although this is not as well documented for PA as for quinidine.
Coadministration of cimetidine decreases renal clearance of PA, potentially leading to clinically significant increases in plasma concentrations. Large (> 300 mg/day) doses of ranitidine possibly have this effect also. Plasma PA concentrations higher than those for administration of PA alone have been reported for coadministration with either amiodarone or trimethoprim. Alcohol (ethanol) consumption tends to decrease the half-life of PA in the blood through induction of its acetylation to NAPA.
Patients taking PA who require neuromuscular blocking agents such as succinylcholine may require less than usual doses of the latter, due to PA effects of reducing acetylcholine release.

Drug/Laboratory Test Interactions: Suprapharmacologic concentrations of lidocaine and meprobamate may inhibit fluorescence of PA and NAPA, and propranolol shows a native fluorescence close to the PA/NAPA peak wavelengths, so that tests which depend on fluorescence measurement may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with PA. It also is not known whether PA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PA should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Both PA and NAPA are excreted in human milk, and absorbed by the nursing infant. Because of the potential for serious adverse reactions in nursing infants, a decision to discontinue nursing or the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Clinical studies of procainamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to the drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function by calculating creatinine clearance and to monitor the plasma levels of procainamide and its major metabolite, N-acetyl procainamide

ADVERSE REACTIONS

Cardiovascular System: Hypotension following oral PA administration is rare. Hypotension and serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common after intravenous administration (see OVERDOSAGE , WARNINGS). Second degree heart block has been reported in 2 of almost 500 patients taking PA orally.

Multisystem Effects: A lupus erythematosus-like syndrome of arthralgia, pleural or abdominal pain, and sometimes arthritis, pleural effusion, pericarditis, fever, chills, myalgia, and possibly related hematologic or skin lesions (see below) is fairly common after prolonged PA administration, perhaps more often in

patients who are slow acetylators (see Boxed Warning and PRECAUTIONS). While some studies have reported less than 1 in 500, others have reported this syndrome in up to 30% of patients on long-term oral PA therapy. If discontinuation of PA does not reverse the lupoid symptoms, corticosteroid treatment may be effective.

Hematologic System: Neutropenia, thrombocytopenia, or hemolytic anemia may rarely be encountered. Agranulocytosis has occurred after repeated use of PA, and deaths have been reported (see WARNINGS and Boxed Warning).

Skin: Angioneurotic edema, urticaria, pruritus, flushing, and maculopapular rash have also occurred occasionally.

Gastrointestinal System: Anorexia, nausea, vomiting, abdominal pain, bitter taste, or diarrhea may occur in 3 to 4 percent of patients taking oral procainamide.

Elevated Liver Enzymes: Elevations of transaminase with and without elevations of alkaline phosphatase and bilirubin have been reported in patients taking oral procainamide. Some patients have had clinical symptoms (eg, malaise, right upper quadrant pain). Deaths from liver failure have been reported.

Nervous System: Dizziness or giddiness, weakness, mental depression, and psychosis with hallucinations have been reported occasionally.

OVERDOSAGE

Progressive widening of the QRS complex, prolonged Q-T and P-R intervals, lowering of the R and T waves, as well as increasing A-V block, may be seen with doses which are excessive for a given patient. Increased ventricular extrasystoles or even ventricular tachycardia or fibrillation may occur. After intravenous administration but seldom after oral therapy, transient high plasma concentrations of PA may induce hypotension, affecting systolic more than diastolic pressures, especially in hypertensive patients. Such high levels may also produce central nervous depression, tremor, and even respiratory depression.
Plasma levels above 10 mcg/mL are increasingly associated with toxic findings, which are seen occasionally in the 10 to 12 mcg/mL range, more often in the 12 to 15 mcg/mL range, and commonly in patients with plasma levels greater than 15 mcg/mL. A single oral dose of IR PA 2000 mg may produce overdosage symptoms, while 3000 mg of IR PA may be dangerous, especially if the patient is a slow acetylator, has decreased renal function, or underlying organic heart disease.
Treatment of overdosage or toxic manifestations includes general supportive measures, close observation, monitoring of vital signs and possibly intravenous pressor agents, and mechanical cardiorespiratory support. If available, PA and NAPA plasma levels may be helpful in assessing the potential degree of toxicity and response to therapy. Both PA and NAPA are removed from the circulation by hemodialysis but not peritoneal dialysis. No specific antidote for PA is known.

DOSAGE AND ADMINISTRATION

The dose should be adjusted for the individual patient, based on clinical assessment of the degree of underlying myocardial disease, the patient's age, and renal function. For patients who have been receiving another formulation of procainamide, the dose of the other formulation can function as a general guide, but re-titration with Procanbid is recommended.

As a general guide, for younger patients with normal renal function, an initial total daily oral dose of up to 50 mg/kg of body weight of Procanbid tablets may be used, given in 2 divided doses, every 12 hours, to maintain therapeutic blood concentrations. For older patients, especially those over 50 years of age, or for patients with renal, hepatic, or cardiac insufficiency, lesser amounts or longer intervals may produce adequate blood concentrations, and decrease the probability of occurrence of dose-related adverse reactions.

CARE SHOULD BE TAKEN WHEN DISPENSING PROCANBID TO ASSURE THE BID DOSAGE FORM HAS BEEN PRESCRIBED AND DISPENSED. Procanbid tablets should be swallowed whole and should not be bitten or cut.

To provide up to 50 mg/kg of body weight per day *	
Patients Weighing	**Dose**
88-110 lb (40-50 kg)	1000 mg q12 hrs
132-154 lb (60-70 kg)	1500 mg q12 hrs
176-198 lb (80-90 kg)	2000 mg q12 hrs
>220 lb (>100 kg)	2500 mg q12 hrs

*Initial dosage schedule guide only, to be adjusted for each patient individually, based on age, cardiorenal function, blood concentration (if available), and clinical response.

HOW SUPPLIED

Procanbid tablets are supplied as follows:

500 mg: White, film-coated, elliptical tablets, coded "PROCANBID" on one side and "500" on the other.
N 61570-069-60 Bottles of 60
N 61570-069-70 Unit dose packages of 100 (10 strips of 10 tablets each).

1000 mg: Gray, film-coated, elliptical tablets, coded "PROCANBID" on one side and "1000" on the other.
N 61570-071-60 Bottles of 60
N 61570-071-70 Unit dose packages of 100 (10 strips of 10 tablets each).

Dispense in well-closed containers as defined in the USP.
Store at 20°-25°C (68°-77°F) [see USP].
Rx only.

Distributed by: Monarch Pharmaceuticals, Inc. Bristol, TN 37620
Manufactured by: Warner-Lambert Co Morris Plains, NJ 07950 USA

Rev. 4/00
0562G121